REMARKS/ARGUMENTS

This is in response to the Office Action mailed July 23, 2009 for the above-captioned application. Reconsideration and further examination are respectfully requested.

The specification (Table 7) has been amended to correct typographical errors in the Table.

New claims 35-37 have been added in which it is recited that the RNA molecule is a double stranded molecule, with one strand consisting of Seq ID No. 10. This corresponds to the species Cl-V or CLU-5 as described in the examples.

The Examiner states that the Declaration Under Rule 131 filed with the last response was sufficient. Without conceding that all of the references are prior art, Applicants are not resubmitting a declaration at this time, but will instead address both rejections on the merits.

The claims as pending relate to a specific RNA sequence. The Examiner rejects this single sequence as obvious over a reference that teaches antisense targeted to clusterin, and two combinations of references (Tuschl and Holen, or Tuschl, Fosnaugh and Hammond) that relate generally to siRNA technology but that teach nothing specific about the clusterin target. Since the prior art is properly considered as a whole, Applicants submit that the combined teachings of these secondary references should be considered in assessing whether the invention now claimed is obvious.

The Examiner points to AS ODN #2 of Miyake as targeting the same site as Seq ID No. 10. Applicants point out, however, that Seq ID No. 10 is two bases shorter at the 5' end than AS ODN #2.

Furthermore, the Examiner has not offered any reasoning as to why a person skilled in the art would use antisense as a starting point in developing an siRNA inhibitor with any particular expectation of success. Applicants submit that the references would not support such an argument.

The mechanism of action of antisense molecules and siRNA molecules is understood to be quite different. As outlined in Hammond, Figure 1, the activity of siRNA involves the formation of a RISC which in turn causes enzymatic destruction of mRM|NAs recognized by the siRNA guide within the RISC. Antisense DNA does not associate in a RISC type complex, and therefore the steric constraints on association with the target are different.

Tuschl also describes the mechanism of siRNA action, and makes extensive reference to target-specific RNA interference, the reference does not contain any particular guidelines on the selection of target sites within a target gene sequences. It is to be noted, however, that the sequences tested in Fig. 1 start at 93 or more bases after the start codon, which clearly does not suggest the selection of Seq. ID No. 10 for clusterin.

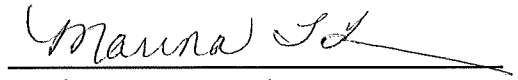
Fosnaugh does, as stated by the examiner, provide in example 3 a protocol for selecting siRNA target sites. The Examiner has not, however, shown that applying the methodology of Fosnaugh would result in the selection of Seq. ID No. 10. In this regard, it is noted that Seq ID No. 10, does not meet the requirements of step 7 (¶ 24) of Fosnaugh.

Holen teaches that "sites in mRNA targets are differentially accessible to ribozymes and oligodeoxynucleotides" (p. 1757, Col. 2) and tested whether position effects were important for siRNA. The reference selected siRNA based on ribozyme accessibility (p. 1758, Col. 2), not antisense accessibility. Furthermore, Holen discloses that siRNA targeting the translation initiation site was "essentially inactive." (*Id.*)

Taking this art as a whole, use of the same region that was targeted by an antisense molecule does not provide a reasonable expectation of success. Characteristics used for selection of siRNA targets would not lead to Seq ID No. 10, and in at least one instance the translation initiation site was found to be a poor choice for siRNA. Thus, the art does not suggest using the antisense target site of Miyake as a target site for RNAi. There is therefore no prima facie case of obviousness with respect to the claimed invention.

For this reason, Applicants submit that the claims of this application are in form for allowance, and that the method claims should be recombined. Favorable reconsideration is respectfully urged.

Respectfully submitted,



Marina T. Larson, Ph.D
Attorney/Agent for Applicant(s)
Reg. No. 32038
(970) 262-1800